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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 2,010.00

Complete if Known	
Application Number	09/210,995
Filing Date	December 15, 1998
First Named Inventor	Sheena M Loosmore
Examiner Name	Ja-Na Hines
Art Unit	1645
Attorney Docket No.	1038-844MIS

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-0244

Deposit Account Name: Aventis Pasteur

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X =
Independent Claims		- 3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex *parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	2,010.00
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 2,010.00

(Complete *if applicable*)

SUBMITTED BY					
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Signature	Robert Yoshida			Date	July 19, 2004

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PATENT Docket No.: 1038-844

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Loosmore, et al.
Application No.:		09/210,995
Filing Date	:	December 15, 1998
Title	:	Multi-Component Vaccine Comprising At Least Two Antigens From Haemophilus influenzae To Protect Against Disease
Grp./AU	:	1645
Examiner	:	Ja-Na Hines

July 19, 2004

APPEAL BRIEF

Dear Sir:

Introduction

This Appeal Brief was timely submitted pursuant to applicant's appeal from a Final Rejection of claims 6-24 dated October 22, 2002. A Notice of Appeal was filed on April 22, 2003.

A Notification of Non-Compliance with 37 CFR 1.192(c) was mailed January 23, 2004 requiring Applicants to file in triplicate a complete new brief in compliance with 37 CFR 1.192(c). In particular, the notice stated that "the brief includes the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet does not present arguments in support thereof in the argument section of the brief." Three copies of a new Appeal Brief are attached. Applicants believe the new Appeal Brief is in compliance with 37 CFR 1.192(c)(7).

(1) **Real Party of Interest**

The real party of interest with respect to this patent application is Aventis Pasteur Limited. Assignments from the inventors to Aventis Pasteur Limited are recorded at Reel 010239/0462 on December 15, 1998.

(2) **Related Appeals and Interferences**

The appellants, the appellants' legal representatives and assignee, are unaware of any pending appeals or interferences which will directly affect or be affected by or have a bearing on the Board's decision in the pending appeal.

(3) **Status of Claims**

This application was filed with claims 1-24. In the response dated September 10, 1999 to the Office Action of April 13, 1999 claims 1 and 22 were amended.

Claims 1-24 were finally rejected in an Office Action dated October 14, 1999. Claims 1-5 were cancelled in a reply brief dated October 19, 2001. Claims 6 to 24 are pending and the subject of this appeal and appear in Appendix I hereto.

(4) **Status of Amendments**

This application was filed with claims 1-24. Claims 6-24 are pending and no amendments were filed subsequent to this final rejection.

(5) **Summary of Invention**

The present invention is directed to an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae,* including otitis media. The composition comprises at least two different antigens of *Haemophilus influenzae,* a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae,* particularly an HMW 1 or HMW 2 protein of the non-typeable strain (page 5, lines 19 to 23), and an analog of *Haemophilus influenzae* Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protein (page 5, line 24 to 31). The invention is further directed to compositions were HMW protein is present in an amount which enhances the immune response in the host to the Hin47 protein and while the individual immunogenicities of the proteins in the composition is not impaired. The Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protein can have specific amino acid mutations to achieve this, claims 9-14. The HMW 1 or HMW 2 protein can be produced recombinantly (claim 16) or from specific strains (claim 17). The composition of the present invention can further comprise an adjuvant (claim 18 and 19) and the components can be in specific quantities of about 25 to about 100 μg of the Hin47 protein analog, and about 25 to about 100 μg of the HMW protein (claim 20). The invention is also directed towards methods of

immunizing a host against disease caused by infection with *H. influenzae* (claim 24).

(6) Issues

The sole issue for consideration is the rejection of claims 6 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp et al in view of Loosmore et al.

(7) Grouping of Claims

All claims do not stand or fall together. Claims 7, 8 and 20 are believed to be separately patentable both from each other and the remaining claims.

(8) Argument

(a) Background to the Invention

Haemophilus influenzae is the cause of several serious human diseases, such as meningitis, epiglottitis, septicemia and otitis media. There are six serotypes of *H. influenzae*, designated a to f, that are identified by their capsular polysaccharide. *H. influenzae* type b (Hib) was a major cause of bacterial meningitis until the introduction of several Hib conjugate vaccines in the 1980's. Vaccines based upon *H. influenzae* type b capsular polysaccharide conjugated to diphtheria toxoid, tetanus toxoid, or *Neisseria meningitidis* outer membrane protein have been effective in reducing *H. influenzae* type b-induced meningitis. The other serotypes of *H. influenzae* are associated with invasive disease at low frequencies, although there appears to be an increase in the incidence of disease caused by these strains as the incidence of Hib disease declines. Non-encapsulated or non-typeable *H. influenzae* (NTHi) are also responsible for a wide range of human diseases including otitis media, epiglottitis, pneumonia and tracheobronchitis. The incidence of NTHi induced disease has not been affected by the introduction of the Hib vaccines.

Otitis media is the most common illness of early childhood, with 60 to 70% of all children, of less than 2 years of age, experiencing between one and three ear infections. Chronic otitis media is responsible for hearing, speech and cognitive impairments in children. *H. influenzae* infections account for about 30% of the cases of acute otitis media and about 60% of chronic otitis media. In the United States alone, treatment of otitis media costs between 1 and 2 billion dollars per year for antibiotics and surgical procedures, such as tonsillectomies, adenoidectomies and insertion of tympanostomy tubes. It is estimated that an additional $30 billion is spent per annum on adjunct therapies, such as speech therapy and special education

classes. Furthermore, many of the causative organisms of otitis media are becoming resistant to antibiotic treatment. An effective prophylactic vaccine against otitis media is thus desirable.

(b) The Present Invention

Having regard to the above Background, it would be desirable to provide efficacious combination vaccines comprising *H. influenzae* components containing selected relative amounts of selected antigens. The present invention provides an immunogenic composition for conferring protection in a host against disease caused by infection with *H. influenzae*, including otitis media.

The immunogenic composition comprises at least two different antigens of *H. influenzae*, one of which is a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* and the other of which is an analog of *Haemophilus influenzae* Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protein as claimed in claim 6, and all claims dependant thereon.

Claim 7 recites that the HMW protein is present in an amount which enhances the immune response in the host to the Hin47 protein. Claim 8 recites that the HMW protein is present in the recited amount while the individual immunogenicities of the proteins in the composition is not impaired. The applicants data supports such results.

(c) Grouping of Claims.

Claims 7, 8 and 20 are believed to be separately patentable both from each other and the remaining claims (i.e., claims 6, 9-19 and 21-24). Claims 7 is dependent on claim 6 and adds the further limitation that "said HMW protein is present in said composition in an amount which enhances the immune response in the host to the Hin47 protein." Claim 8 depends on claim 7 and adds the further limitation that "said HMW protein is present in the said amount while the individual immunogenicities of the proteins in the composition is not impaired." Claim 20 depends on claim 6 and adds the further limitation that the composition comprises "about 25 to about 100 μg of the Hin47 protein analog, and about 25 to about 100 μg of the HMW protein."

Claims 7, 8 and 20 are separately patentable both from each other and the remaining claims because each contains a different further limitation relating to the concentrations of a HMW protein and Hin47 protein which distinguishes these claimed compositions from the compositions defined by the remaining claims as well as from each other. The compositions of claims 7, 8 and 20 each provide a surprising result in view of the

phenomenon of antigenic interference observed by Applicants with a composition comprising certain concentrations of HMW protein and Hin47 protein as is discussed directly below. In view of the arguments discussed directly below, the compositions of claims 7, 8 and 20 are separately patentably both from each other and the remaining claims.

(d) Rejection of claims 6-24 under 35 USC 103(a).

Claims 6 to 24 have been finally rejected under 35 USC 103(a) as being unpatentable over Barenkamp (WO 87/36914) in view of Loosmore. Barenkamp teaches high molecular weight proteins of non-typeable *H. influenzae* identified as HMW1, HMW2, HMW3 and HMW4, which are characterized by molecular weight and sequence information. Loosmore et al teach an analog of *H. influenzae* Hin47 protein with reduced protease activity. It is submitted that these references lack any motivation to combine two different antigens of *H. influenzae,* namely a non-proteolytic Hin47 protein of Loosmore et al with the HMW proteins of Barenkamp et al in an immunogenic composition. Claim 6 defines an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae,* which comprising two components, namely:

an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than 10% of that of natural Hin47 protein, and a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae.* Thus, particularly in quantities where the immune response of the Hin47 protein is enhanced by the HMW protein (claim 7) and in which the individual immunogenicities of the proteins is not impaired (claim 8).

The Barenkamp et al reference describes the HMW protein while the Loosmore et al reference describes the non-proteolytic Hin47 analog. It is the applicants position that neither reference provides the motivation to combine the two immunogens in a single composition as required by claim 6, and by dependency all claims on appeal.

As the Examiner points out, both references contain the statement:

> "The immunogenic composition of the invention may further comprise at least one other immunogenic or immunostimulating material" (Barenkamp, p. 7,111 to 5; Loosmore, col. 3,11 63 to 65).

The only "immunogenic or immunostimulating material" identified is an adjuvant, suggesting that the latter materials are preferred additional components, rather than an immunogenic

material. In any event, there is no immunogenic material particularly specified in either reference and neither does the Examiner suggest that there is.

The two references also contain the statement:

> "A vaccine which contains antigenic material of only one pathogen is a monovalent vaccine. Vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain, for example, material from various pathogens or from various strains of the same pathogen or from combinations of various pathogens" (p. 22, II 1 to 8 of Barenkamp; p. 9, II 14 to 19 of Loosmore).

While suggesting various combinations, there is no suggestion here to combine different proteins derived from the same pathogen, as in applicants claim 6. Again, the references are silent as to any specific combination contemplated.

The Examiner's view is best summarized by the statement in the Office Action that:

> "No more than routine skill was required at the time of appellants invention to combine two well-known compositions, i.e. two different antigens of *H. influenzae,* each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for that very same purpose of providing an immunogenic composition."

However, the cited prior art lacks the motivation to do so. As noted above, there are vague, non-specified indications in both references to combine other components with the specific immunogen, but there is no specific indication as to what that other component may comprise, other than an adjuvant (first quotation above) or materials from the pathogens and/or materials from various strains of the same pathogen (second quotation above).

As the Examiner has pointed out, on page 49, lines 15 to 19 of Barenkamp, it is stated:

> "... the data suggests the HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI vaccine."

This passage appears to suggest that only *Haemophilus* proteins which are the HMW adhesin proteins are appropriate components. The non-proteolytic analog of Hin47 is not an adhesin (although initially thought to be adhesin, see col. 2, line 17 of Loosmore et al). (It is pointed out that the Examiner is incorrect in the statement that the adhesin protein "should" comprises one component of the NTHI vaccine. As can be seen from the above quotation, Barenkamp uses the word "may").

Even if the Examiner finds motivation in this passage of Barenkamp to combine the HMW protein with another *Haemophilus* antigen, whether an adhesin or not, such motivation still provides no motivation to select the non-proteolytic Hin47 analog as the other *Haemophilus* antigen.

There have been a significant number of *Haemophilus* proteins identified as vaccine candidates besides the HMW and Hin47 analog proteins. These proteins include the various outer membrane proteins A to H, lactoferrin and transferrin receptor protein and the P1, P2, P6 and D15 proteins. It is submitted that there is no motivation provided by the cited prior art why a person skilled in the art would specifically select from all the optional possibilities, the non-proteolytic Hin47 analog to specifically combine with the HMW protein.

The Examiner states in the Office Action, quoting In re Kerkhoven, that:

> "The idea of combining them flows logically from their having been individually taught in the prior art."

The "idea of combining them" does not explain why the two materials should be combined when there is selection available. If the two antigens were the only two known antigens of *Haemophilus influenzae*, then there may be some validity to the position taken by the Examiner, but this is clearly not the case here.

In any event, caution is required when considering combining different antigens into immunogenic compositions because of the danger of impairment of the immunogenicity of the individual components one by the other. As may be seen from Applicants data, this

phenomenon was observed for increasing amounts of H91A Hin47 when combined with a low dose of HMW, but disappeared at higher doses of HMW (see Figure 3).

The Examiner indicates in the Office Action that:

"Applicant neither argues, nor shows scientific data teaching unexpected results".

It is submitted that such is not the case. Applicants data clearly shows that a synergistic effect can be achieved both in response to the HMW and H91A Hin47 by combining them. Thus, there is a synergistic effect observed for increasing amounts of HMW on the primary antibody response to a low dose of H91A Hin47. The H91A H47 improved the primary response to HMW, if the HMW was not present in low doses.

It is submitted that these findings are a surprising result. In addition, it is further surprising that HMW would enhance the vigorous antibody response to H91A Hin47, since it is a weaker immunogen.

Furthermore, these results are unexpected in the field of combination vaccines. There is little expectation of success that simply mixing existing vaccine antigens will not result in incompatibilities amongst the various antigens, resulting in loss of stability or reduced potency or indeed a synergistic effect increasing potency. Immune interference cannot be predicted. Others skilled in the art of combination vaccines have found that the preparation of combination vaccines is far from straight forward. For example Cauldfield et al (2001) report on the need for a balanced formulations of vaccine components in the preparation of DTP combination vaccines to circumvent interference with the components. Van den Bosch et al (2003) have also reported that the addition of a potential antigen (Pal A) from A. pleuropneumoniae can completely eliminate the positive efficacy of known antigens (ApxI and II) when combined (see abstract).

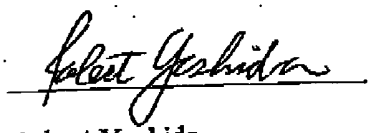
For all these reasons, it is submitted that claims 6 to 24 are patentable over the applied art and the rejection thereof under 35 USC 103(a) as being unpatentable over Barenkamp in view of Loosmore et al.

(11) Summary

Having regard to the above detailed discussion, it is submitted that the Examiner is in error in rejecting claim 6 to 24 as being unpatentable and hence the rejection thereof under 35 USC 103(a) as being unpatentable over the combination of Barenkamp (WO 97/36914) in

view of Loosmore et al, should be REVERSED.

Respectfully submitted,



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APPENDIX I

CLAIMS APPEALED (09/210,995)

6. An immunogenic composition for conferring protection in a host against disease caused by *Haemophllus influenzae*, which comprises:
an analog of *Haemophllus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein, and a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae*.

7. The composition of claim 6 wherein said HMW protein is present in said composition in an amount which enhances the immune response in the host to the Hin47 protein.

8. The composition of claim 7 wherein said HMW protein is present in the said amount while the individual immunogenicities of the proteins in the composition is not impaired.

9. The composition of claim 6 wherein said analog of Hin47 protein is one in which at least one amino acid of the natural Hin47 protein contributing to protease activity has been deleted or replaced by a different amino acid and which has substantially the same immunogenic properties as natural Hin47 protein.

10. The composition of claim 9 wherein said at least one amino acid is selected from the group consisting of amino acids 91, 121 and 195 to 201 of natural Hin47 protein.

11. The composition of claim 10 wherein Serine-197 is replaced by alanine.

12. The composition of claim 10 wherein Histidine-91 is replaced by alanine, lysine or arginine.

13. The composition of claim 12 wherein Histidine-91 is replaced alanine.

14. The composition of claim 10 wherein Asp-121 is replaced by alanine.

15. The composition of claim 8 wherein said HMW protein is an HMWI or HMW2 protein of a non-typeable strain of *Haemophilus influenzae*.

16. The composition of claim 15 wherein the HMW1 and HMW2 proteins are produced recombinantly.

17. The composition of claim 15 wherein said HMW1 and HMW2 proteins are derived

from the respective strain of non-typeable *Haemophilus influenzae* and possess respective molecular weights as set forth in the following Table:

Molecular Weight (kDa)	Non-typeable *H. influenzae* Strain					
	12	JoyC	K21	LCDC2	PMH1	15
Mature Protein: HMW1	125	125.9	104.4	114.0	102.4	103.5
HMW2	120	100.9		111.7	103.9	121.9

18. The composition of claim 6 further comprising an adjuvant.

19. The composition of claim 18 wherein said adjuvant is aluminum hydroxide or aluminum phosphate.

20. The composition of claim 6 comprising about 25 to about 100 μg of the Hin47 protein analog, and about 25 to about 100 μg of the HMW protein.

21. The composition of claim 6 further comprising at least one additional antigenic component for conferring protection against infection caused by another pathogen.

22. The composition of claim 6 wherein said at least one additional antigenic component is selected from the group consisting of diphtheria toxoid, tetanus toxoid, pertussis antigens, non-virulent poliovirus and a conjugate of a tetanus or diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae*.

23. The composition of claim 22 wherein said pertussis antigens are selected from the group consisting of pertussis toxoid, filamentous hemagglutinin, pertactin and agglutinogens.

24. A method of immunzing a host against disease caused by infection with *Haemophius influenzae*, including otitis media, which comprises administering to the host an immunoeffective amount of a composition as claimed in claim 6.